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(71) Applicant: DERMATOLOGICAL PRODUCTS OF TEXAS [US/US]; 6201 South Freeway, P.O. Box 1959, Fort Worth, TX 76101 (US).

(72) Inventors: HEBBORN, Peter ; 5500 Grissom Drive, Arlington, VA 76016 (US). ACHARYA, Ramesh, N. ; 7117 Bettis Drive, Fort Worth, TX 76133 (US). BIDGOOD, Alison : 1140 Woodvale Drive, Bedford, TX 76021 (US). PATEL, Dinesh, C., 5839 South Meadow Crest Drive, Murray, UT 84107 (US).

(74) Agent: PRICE, Robert, L.; Lowe, Price, Leblanc, Becker & Shur, 427 North Lee Street, Alexandria, VA 22314 (US).

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(54) Title: FILM-FORMING, PHARMACEUTICAL VEHICLES FOR APPLICATION OF MEDICAMENTS TO NAILS, PHARMACEUTICAL COMPOSITIONS BASED ON THOSE VEHICLES, AND METHODS OF USING SAME

(57) Abstract

Film-forming, pharmaceutical vehicles containing hydrophilic, polymeric resins, pharmaceutical compositions based on the vehicles, and methods of treating onychopathic conditions using the compositions. The vehicles form continuous, self-supporting films when applied to human nails and do not disintegrate when contacted with water, thereby enabling compositions based on the vehicles to deliver drugs to the nails over extended periods of twenty-four hours or l nger with only a single application of the compositions.

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FILM-FORMING, PHARMACEUTICAL VEHICLES FOR APPLICATION OF MEDICAMENTS TO NAILS, PHARMACEUTICAL COMPOSITIONS BASED ON THOSE VEHICLES, AND METHODS OF USING SAME

Background of the Invention

1. Field of the Invention

The present invention relates to film-forming vehicles for delivering medicaments to the nails of mammals. More particularly, this invention relates to film-forming vehicles which are adapted to deliver one or more active ingredients to human nails in the treatment of various onychopathic conditions, such as onychomycosis. These vehicles provide a means for topical treatment of onychopathic conditions that is both effective and convenient. This invention also relates to pharmaceutical compositions based on such vehicles and to a method of treating onychopathic conditions using these compositions.

2. Discussion of Related Art

Onychopathic conditions are very difficult to treat topically due to the poor delivery of drugs through the nails when the drugs are applied using conventional dosage forms, such as, creams, lotions, gels, solutions, and so on. This poor delivery is primarily attributable to the fact that the drugs are easily rubbed off, washed away or otherwise removed from the nails when applied via the conventional dosage forms mentioned above, and as a result may only be in contact with the nails for a very limited time.

Human nails are typically 100 to 200 times thicker than the stratum corneum. Because of this greater thickness, the time required for a given quantity of drug to penetrate the nail is much greater than the time required for the same quantity of drug to penetrate the stratum corneum. Thus, the drug must be in contact with the nail for a relatively long time (e.g., several hours) in order to achieve a therapeutic concentration of drug in the affected tissue beneath the nail (i.e., the nail bed). The above-cited conventional dosage forms are generally ineffective because the drug is not kept in contact with the nail long enough to achieve a therapeutic concentration of drug in the nail bed.

The prior art approaches to treating onychopathic conditions have generally fallen into one of three categories. Namely, these approaches have relied on either systemic (e.g., oral) administration of drugs; surgical removal of all or part of the nail followed by topical application of drugs to the thus exposed tissue beneath the nail; or topical application of conventional creams, lotions, gels or solutions, frequently including the use of bandages to keep these dosage forms in place on the nails. All of these prior art approaches suffer from major drawbacks.

A major problem seen with systemic therapy is the considerable amount of time which is usually required to produce a therapeutic effect in the nail bed. For example, oral treatment of onychomycoses with the antifungal compound ketoconazole typically requires administration of a 200 to 400 mg daily dose for an average period of 20-25 weeks before any significant therapeutic effect is realized. The potential for side effects on major organ systems is a very significant danger associated with such long term, systemic therapy, since ketoconazole has been reported to produce fatalities attributable to liver toxicity and to reduce testosterone levels in the blood due to an adverse effect on the testes. A further drawback seen with this type of therapy is the greater expense to the patient and consequent adverse affect on patient compliance.

A major drawback seen with the second type of therapy mentioned above, namely removing all or part of the nail prior to topical treatment of the condition, is the discomfort experienced by the patient, both during and subsequent to removal of the nail. A further problem with this approach is the undesirable cosmetic appearance of the nail or nail bed; this may represent a significant problem for some patients, particularly female patients.

A major problem seen with the third prior art approach to therapy has already been mentioned above; namely, conventional dosage forms such as creams, lotions, gels or solutions are easily removed from the nails. The use of bandages or similar means in an attempt to eliminate this problem has generally been met with poor patient compliance. The poor patient compliance is understandable, since such bandages are

typically awkward and become very troublesome to keep in place over extended periods of several weeks or more. The use of a 2% miconazole cream together with occlusive bandages to treat onychomycosis is discussed in the following article: E. Heinke, "Clinical experiences with miconazol with special regard to a conservative treatment of the onychomycoses and paronychia", Mykosen, Vol. 15, pp. 405-407 (1972).

A 2% miconazole alcoholic solution is described in the following article: J. Vanderdonckt et al., "Miconazole alcoholic solution in the treatment of mycotic nail infections", Mykosen, Vol. 19, pp. 251-256 (1976). The solution is said to have the following formula:

Miconazole base	0.2 gram
Carbosept No. 525	0.475 gram
Carbosept No. 515	0.025 gram
Propylene glycol USP	2 gram
Ethanol USP	ad 10 mL

The article characterizes the above-identified solution as being a "film-forming alcoholic solution." (Emphasis added.) However, experiments conducted by the present inventors have shown that in fact the vehicle utilized by Vanderdonckt et al., (i.e., all of the ingredients listed above except for the miconazole) does not produce a continuous, self-supporting film, but rather leaves a deposit on the nails which may be more readily described as a residue than as a film. For purposes of the present specification, a film is considered to be self-supporting when it can be peeled from a nonstick surface such as glass or Teflon®. That is, a film is considered to be self-supporting when it can be removed from a nonstick surface and still retain the physical characteristics and form of a continuous film.

The experiments conducted by the present inventors have shown that the residue formed by the above-identified solution takes several hours to dry and disintegrates if placed in water. In contrast, the film-forming vehicles of the present invention generally require only a few minutes to dry when placed on human nails and do not disintegrate readily when contacted with water. These properties of the film-

forming vehicles of the present invention are very significant with respect to the patient compliance and efficacy seen with compositions based on these vehicles.

The above-cited article also states that the solution was applied to the nails in drop form twice daily. This is a further indication that the alcoholic solution utilized by Vanderdonckt et al., is significantly different from the film-forming vehicles of the present invention, which form a continuous film, adhere readily to the nail, and may be applied as infrequently as once or twice per week. Additional reports on the use of the above-identified 2% miconazole alcoholic solution are set forth in the following articles: G. Achten et al., "Treatment of onychomycosis with a solution of miconazole 2% in alcohol," Mykosen, Vol. 20, pp. 251-256 (1976); and B. Bentley-Phillips, "The treatment of onychomycosis with miconazole tincture," South African Medical Journal, Vol. 62, pp. 57-58 (1982).

Japanese Patent Application No. 58-92926 (preliminary publication No. 59-216822) discloses film-forming, endermic formulations. Those formulations differ from the film-forming vehicles of the present invention in that, among other things, the films formed are specially adapted to be flexible so as to remain on the skin after drying. A considerable amount (i.e., 5 to 1500 parts by weight) of a plasticizer (e.g., propylene glycol) is included in the formulations in order to provide this flexibility. It is believed that these formulations would require a considerable amount of time to dry if painted on human nails due to the relatively large amount of plasticizer contained therein. The film-forming vehicles of the present invention are specially adapted for use on nails rather than skin, and do not require the presence of a plasticizer in order to provide flexibility. Thus, the film-forming vehicles of the present invention are designed to form films which are relatively inflexible compared to those of the type described in the Japanese Application.

The foregoing discussion demonstrates that a need exists for an effective, topical regimen for treating onychopathic conditions. More

specifically, a need exists for an effective means of applying drugs topically to the nails in a manner which will, among other things, bring about:

(1) prolonged presence of drug on the nails;

(2) relatively rapid therapeutic concentrations of drug in the nail bed; and

(3) improved patient compliance based on convenience and cosmetic appearance.

This need has provided the stimulus for the present invention.

Summary of the Invention

A principal object of the present invention is the provision of film-forming vehicles adapted to deliver drugs to nails in an efficacious and cosmetically acceptable manner.

A further object of this invention is the provision of film-forming vehicles which significantly enhance the delivery of drugs through nails by maintaining the drugs in contact with the nails.

A still further object of this invention is the provision of pharmaceutical compositions based on such film-forming vehicles, and a method of treating onychopathic conditions utilizing these compositions.

The foregoing objects and other general objects of the present invention are satisfied by the provision of a pharmaceutical vehicle adapted to deliver drugs to the nails which comprises from about 2% to about 40% by weight of a hydrophilic, film-forming resin, and a pharmaceutically acceptable solvent for said resin, said vehicle being capable of forming a continuous, self-supporting film when applied to human nails, and pharmaceutical compositions based on such vehicles.

Description of Preferred Embodiments

The film-forming vehicles of the present invention are based on hydrophilic, film-forming resins. The film-forming resins utilized in this invention are polymeric materials which are at least partially soluble in water and/or polar organic solvents (e.g., methanol, ethanol, isopropanol, acetone, chloroform, methylene chloride, and so on), and which are capable of producing a continuous, self-supporting

film upon evaporation of the solvent. As mentioned above, the films formed by the vehicles of the present invention are considered to be self-supporting because it is possible to remove the films from a nonstick surface and still retain the physical characteristics and form of a continuous film. The film-forming resins are hydrophilic in the sense that they have an affinity for water or polar organic solvents, and are wettable by water. Examples of such film-forming resins include: cellulose resins, ethylene oxide resins, acrylic acid and acrylate resins, vinyl resins and vinyl pyrrolidone resins.

Examples of suitable cellulose resins include: methyl cellulose, carboxymethyl cellulose, hydroxypropylcellulose, hydroxypropylmethyl cellulose and hydroxyethylcellulose.

Examples of suitable ethylene oxide resins include polyethylene oxide polymers.

Examples of suitable acrylic acid and acrylate resins include: polyacrylamide, polyacrylic/polymethacrylic, polymethacrylate/butyl-acrylate, polyacrylic/acrylate and polyacrylic acid polymer.

Examples of suitable vinyl resins include: polyvinyl alcohol and poly (methyl vinyl ether/maleic anhydride).

Examples of suitable vinyl pyrrolidone resins include: polyvinyl pyrrolidone, polyvinyl pyrrolidone/vinyl acetate, and vinyl pyrrolidone/dimethylaminethyl methacrylate.

The above-described hydrophilic, film-forming resins are commercially available. The resins which may be utilized in the present invention are further illustrated by the specific examples set forth in Table 1 below.

Table 1

Class	Subclass	Tradename	Manufacturer	Molecular Weight Range
Cellulose Resins	Alkyl Cellulose	Methocel A	Dow Chemical	50,000 - 1,000,000
	Hydroxyakyl Alkyl Cellulose	Methocel E	Dow Chemical	
	Carboxymethyl Cellulose	CMC	Industries of India	50,000 - 700,000
		CMC-T	Hercules Chemicals	
	Hydroxy Alkyl Cellulose	HEC HPC Klucel Natrosol	Hercules Chemicals	50,000 - 1,200,000
Ethylene Oxide Resins	Polyethylene Oxide Polymers	Polyox WSR N-10 Polyox WSR N-80 Polyox WSR N-750 Polyox WSR N-3000 Polyox WSR 205 Polyox WSR 1105 Polyox WSR 301	Union Carbide	50,000 - 4,000,000

Continued . . .

Table 1 - Continued

Class	Subclass	Tradename	Manufacturer	Molecular Weight Range
Acrylic Acid and Acrylate Resins	Poly (acrylic acid)	*Acrysol-1 *Acrysol-3 *Acrysol-5	Rohm and Haas	50,000 - 400,000
		Carbopol 910 Carbopol 934 Carbopol 940 Carbopol 941	B. F. Goodrich	400,000 - 5,000,000
	Polyacrylamide	*Poly Trap 158 *Poly Trap FML 205	Wickhen Chemicals	10,000 - 1,000,000
	Acrylyamide/ Sodium Acrylate	Reten-421 Reten-423 Reten-425	Hercules Chemicals	10,000 - 1,000,000
	Acrylic/Acrylate Copolymer	Carboset-514 Carboset-515 Carboset-525	B. F. Goodrich	7,000 - 1,000,000
	Polymethacrylate/ Butyl Acrylate Copolymer	Plastoid A Plastoid B	Rohm Pharm. Co.	25,000 - 1,000,000
Vinyl Resins	Polyvinyl Alcohol	Gohsenol Gelvatol Elvanol	Nippon Gohesie Monsanto E. I. DuPont	25,000 - 300,000

Continued . . .

Table 1 - Continued

Class	Subclass	Tradename	Manufacturer	Molecular Weight Range
Polyvinyl Pyrrolidone Resins	Polyvinyl Pyrrolidone Polymers	PVP K-25 PVP K-30 PVP K-90	G. A. F. Chemicals	15,000 - 800,000
	Polyvinyl Pyrrolidone/ Vinyl Acetate Copolymers	**PVP/VA	G. A. F. Chemicals	50,000 - 1,000,000
	Polyvinyl Pyrrolidone/ Dimethylamino-ethyl Methacrylate Copolymers	GAFQUAT	G. A. F. Chemicals	100,000 - 1,000,000

*These products are actually formulations containing the indicated type of resin rather than pure resin.

**A series of polyvinyl pyrrolidone/vinyl acetate copolymers containing the following ratios of PVP/VA: 70/30, 60/40, 50/50, 30/70, and 20/80.

The above-identified film-forming, polymeric resins are further described in the following publications: Handbook of Water Soluble Gums and Resins, Davidson, R. L., McGraw-Hill Book Company (1980); and "Gum Technology in the Food Sciences," Food Science and Technology - A Series of Monographs, Glicksman, M., Academic Press (1969). The entire contents of these publications are incorporated herein by reference.

One or more of the above-described hydrophilic, film-forming resins are contained in the film-forming vehicles of this invention in an amount of from about 2% to about 40% by weight. The amount of polymeric resin utilized in specific vehicles will vary depending on factors such as the molecular weight, viscosity and solubility of the resin; the type of solvent utilized; the inclusion of other components in the vehicles; and the type of active ingredient contained in the vehicles. The amount of polymeric resin contained in the vehicles will also depend to some extent on the particular type of resin utilized. The preferred ranges for each of the five classes of resins identified in Table 1 are as follows:

Class	Preferred Range (wt %)
Cellulose Resins	5-15
Polyethylene Oxide Resins	10-30
Acrylic Acid and Acrylate Resins	5-35
Vinyl Resins	10-30
Polyvinyl Pyrrolidone	10-30

The film-forming vehicles described above are optionally used in combination with a layer of polymeric material which is applied to the nail after the film-forming vehicle has dried. The use of this second layer of material in effect creates a two coat system on the nail, with the first coat comprising the film-forming vehicle and drug and the second coat comprising the layer of polymeric material or overcoat.

The two coat system generally enhances the ability of drugs to penetrate the nail by modifying the hydration characteristics of the nails and the film-forming vehicles.

The two coat system is also advantageous in that it generally allows a greater concentration of drug to be contained in the film-forming vehicles. More particularly, when higher concentrations of drug are contained in the film-forming vehicles, the vehicles exhibit a greater tendency to deteriorate when submerged in water. The overcoat layer protects the film-forming vehicles from such deterioration, and thereby enables a greater concentration of drug to be contained in the vehicles.

The overcoat layer should preferably be waterproof, and must be capable of drying quickly (i.e., within 10 to 15 minutes, preferably within 1-2 minutes). Various types of materials meeting these requirements may be utilized. For example, most commercially available nail lacquers and polishes can be utilized for this purpose. This is a distinct advantage in the treatment of many female patients, since the ability to use nail polishes for the overcoat layer in the two coat system may further contribute to good patient compliance by allowing the patient to maintain the normal cosmetic appearance of the nails while undergoing treatment.

Although commercially available nail lacquers and polishes may be utilized for the overcoat layer, the film-forming vehicles of the present invention and solutions containing pyroxylin resin (e.g., collodion USP and flexible collodion USP) may also be utilized for this purpose.

The film-forming vehicles of the present invention may further comprise one or more chemical agents to modify the physical and/or chemical properties of the vehicles and films formed from the vehicles. Examples of physical and chemical properties of the vehicles which may be modified include: solubility of the film-forming resins and drugs, viscosity, suspendability, clarity, light and UV absorption, and drying. Examples of the physical properties of films which may be modified include: elasticity, hardness, brittleness, appearance, adherence, drying and tackiness.

The classes of chemical agents which may be utilized to modify the above-described properties include: humidity controlling agents and tack controlling agents. Examples of suitable tack control agents include: carboxymethyl cellulose, cellulose, cellulose acetate proprionate, colloidal silica and shellac. Examples of suitable humidity controlling agents include glycerin and sorbitol.

The specific chemical agents utilized to modify the above-discussed properties and the amount of such agents required are dependent on numerous factors, but are primarily dependent on the desired drying time of the film. In general, it is desired that the film-forming vehicles of this invention be capable of forming a dry film within 15 minutes following application to the nails, preferably within 5 minutes. The films are deemed "dry" when tack free if touched lightly with a finger.

In addition to the above-described components, the film-forming vehicles of this invention may also include various adjuvants conventionally utilized in topically applied pharmaceutical dosage forms, such as, antioxidants, antimicrobial preservatives, chelating agents, buffering agents, pigments, ultra-violet absorbers, and so on.

The film-forming vehicles described above may be utilized to deliver a wide variety of drugs to the nails. Because of the hydrophilic properties of the resins, films formed from the resins support the diffusion of drugs contained in the film matrix. The only limitations with regard to the types of drugs which may be delivered are that the drug be physically and chemically compatible with the film-forming vehicle and be capable of permeating the nail. With regard to the latter requirement, it has been determined that drugs having a molecular weight of greater than about 550 can not effectively permeate the nail. Accordingly, the drugs which may be utilized in the compositions of the present invention must have a molecular weight less than about 550, and preferably have a molecular weight less than about 300. It has also been determined that drugs having a water solubility of greater than about 0.01 percent by weight generally permeate the nail more readily than drugs having a lesser degree of water

solubility. Drugs having a water solubility of greater than about 0.01 percent by weight are therefore preferred in the present invention.

Two particularly important classes of drugs which are useful in the treatment of onychopathic conditions are anti-inflammatories and anti-mycotics. Other classes of drugs which may be delivered by the vehicles of the present invention include, for example, antibiotics, antineoplastics and antipsoriatics, such as methotrexate.

The antimycotics represent an especially important class of drugs, since fungal infections of nails and nail beds are typically very difficult to treat using conventional prior art therapies. The film-forming vehicles of the present invention are particularly useful for delivering drugs having antimycotic activity to the nails. Specific examples of suitable drugs having antimycotic activity are miconazole, clotrimazole, ketoconazole, econazole, tioconazole, thiabendazole, bifonazole, chlormidazole, ciclopirox, sodium propionate, sodium pyrithione, and pharmaceutically acceptable salts thereof. These drugs are all known compounds which are further described, for example, in The Merck Index, Tenth Edition (1983).

The amount of drug contained in the compositions of the present invention will vary widely depending on the particular type of drug, severity of the condition, and other factors. In general, the compositions will contain from about 0.01% to about 25% by weight of one or more drugs as principal active ingredient.

The present invention is further illustrated by the following examples, but should not be interpreted as being limited in any way by these examples.

Examples 1-2

The following formulations illustrate the film-forming vehicles of the present invention and compositions based on those vehicles which contain a drug having antimycotic activity. All percentages are by weight based on the total weight of the composition.

Example 1

Ingredient	%
Carboset 525	18
Omadine (sodium pyrithione)	1
Purified Water	15
Alcohol (SD 40-2)	QS 100

This composition was prepared by combining all of the ingredients except for the Carboset 525 resin to form a mixture, and then adding the Carboset 525 resin to that mixture. The resulting mixture was stirred with a paddle stirrer until the Carboset 525 resin was dissolved. The resulting product was a clear solution having a straw color. When painted on nails as a thin layer, this product provided a tack-free, transparent film within approximately three minutes following application.

Example 2

Ingredient	%
Carboset 525	18.8
Miconazole Nitrate	1.0
Purified Water, USP	15.6
Alcohol (SD 40-2)	QS 100

This composition was prepared in the manner described in Example 1 above. When painted on nails as a thin layer, this composition provided a tack-free, transparent film within approximately five minutes following application.

Examples 3-4

The following formulations illustrate the film-forming vehicles of the present invention and compositions based on those vehicles which contain a drug having anti-inflammatory activity. All percentages are by weight based on the total weight of the composition.

Example 3

Ingredient	%
Carboset 525	18.0
Ibuprofen	5.0
Purified Water, USP	15.0
Alcohol (SD 40-2)	QS 100

This composition was prepared in the manner described in Example 1 above. When painted on nails as a thin layer, this composition provided a tack-free, transparent film within approximately 3-1/2 minutes following application.

Example 4

Ingredient	%
Carboset 525	18.8
Hydrocortisone	1.0
Purified Water, USP	15.6
Alcohol (SD 40-2)	QS 100

This composition was prepared in the manner described in Example 1 above. When applied on nails as a thin layer, this composition provided a tack-free, transparent film within approximately 5 minutes following application.

Examples 5-7

The following formulations further illustrate the film-forming vehicles of the present invention and compositions based on those vehicles. All percentages are by weight based on the total weight of the composition.

Example 5

Ingredient	%
Polyvinyl Alcohol (Vinyl Resin)	25.0
Sodium Propionate (Antifungal)	1.0
Water	QS 100

This composition may be prepared by dissolving the polyvinyl alcohol in water with stirring and dissolving the sodium propionate in the resulting solution.

Example 6

Ingredient	%
PVP/VA (Polyvinyl Pyrrolidone Resin)	20
Ibuprofen (Anti-inflammatory)	5
Alcohol (SD 40-2)	20
Water	QS 100

This composition may be prepared by dissolving the PVP/VA in the alcohol with stirring, and then slowly adding the ibuprofen and water with stirring.

Example 7

The following formulation illustrates a composition which is suitable for use as the overcoat layer. All percentages are by weight based on the total weight of the composition.

Ingredient	%
Camphor	2
Castor Oil	3
Collodion USP	QS 100

The ingredients are combined and shaken to form a solution.

Example 8

The following experimental results demonstrate the efficacy of the present compositions in treating onychopathic conditions, specifically onychomycoses.

A fifty-two year old, white male patient, afflicted with an onychomycotic infection of the big toe, had treated the infection topically with applications of either Tinactin™ (tolnaftate) solution or Micatin™ (miconazole) cream twice daily for many months without producing any clinical signs of improvement. This patient was treated with a composition in accordance with the present invention containing 5.0 wt.% sodium omadine (sodium pyrithione) and based on the vehicle illustrated in Example 1. The composition was applied to the affected toe by painting a single layer on the nail, and waiting approximately two minutes for the layer to form a dry, tack-free film. The composition was applied in this manner two times per week beginning in October 1984. By December 1984, obvious clinical improvement was apparent based on the growth of a normal appearing toe nail. By June 1985, the nail no longer exhibited any clinical signs of fungal infection.

The present invention has been described above in connection with certain preferred embodiments. However, as variations thereon will become apparent to those skilled in the art, the invention is not to be considered as limited thereto.

What is claimed is:

1. A pharmaceutical vehicle for delivering drugs topically to human nails, comprising from about 2% to about 40% by weight of a hydrophilic, film-forming resin, and a pharmaceutically acceptable solvent for said resin, said vehicle being capable of forming a continuous, self-supporting film when applied to human nails.

2. A pharmaceutical vehicle according to Claim 1, wherein the hydrophilic, film-forming resin is selected from the group consisting of cellulose resins, ethylene oxide resins, acrylic acid and acrylate resins, vinyl resins, and polyvinyl pyrrolidone resins, and the vehicle is capable of forming a dry film within 15 minutes following application to human nails.

3. A pharmaceutical vehicle according to Claim 1, wherein the hydrophilic, film-forming resin comprises from about 5% to about 15% by weight of a cellulose resin.

4. A pharmaceutical vehicle according to Claim 1, wherein the hydrophilic, film-forming resin comprises from about 10% to about 30% by weight of a ethylene oxide resin.

5. A pharmaceutical vehicle according to Claim 1, wherein the hydrophilic, film-forming resin comprises from about 5% to about 35% by weight of an acrylic acid resin.

6. A pharmaceutical vehicle according to Claim 1, wherein the hydrophilic, film-forming resin comprises from about 5% to about 35% by weight of an acrylate resin.

7. A pharmaceutical vehicle according to Claim 1, wherein the hydrophilic, film-forming resin comprises from about 10% to about 30% by weight of a vinyl resin.

8. A pharmaceutical vehicle according to Claim 1, wherein the hydrophilic, film-forming resin comprises from about 10% to about 30% by weight of a polyvinyl pyrrolidone resin.

9. A pharmaceutical composition useful in the treatment of conditions involving human nails, comprising:

a pharmaceutical vehicle comprising from about 2% to about 40% by weight of a hydrophilic, film-forming resin, and a pharmaceutically acceptable solvent for said resin, said vehicle being capable of forming a continuous, self-supporting film when applied to human nails; and

an effective amount of a drug that is chemically and physically compatible with the vehicle and is capable of permeating human nails, said drug having a molecular weight of less than about 550.

10. A pharmaceutical composition according to Claim 9, wherein the hydrophilic, film-forming resin is selected from the group consisting of cellulose resins, ethylene oxide resins, acrylic acid and acrylate resins, vinyl resins, and polyvinyl pyrrolidone resins; the vehicle is capable of forming a dry film within 15 minutes following application to human nails; and the drug has a molecular weight less than about 300 and a water solubility of at least about 0.01 percent by weight.

11. A pharmaceutical composition according to Claim 9, wherein the drug is selected from the group consisting of antibiotics, antimycotics, anti-inflammatories, antipsoriatics and antineoplastics.

12. A pharmaceutical composition according to Claim 9, wherein the drug comprises an antimycotic.

13. A pharmaceutical composition according to Claim 12, wherein the antimycotic drug is selected from the group consisting of miconazole, clotrimazole, ketoconazole, econazole, tioconazole, thiabendazole, bifonazole, chlormidazole, ciclopirox, sodium propionate, sodium pyrithione and pharmaceutically acceptable salts thereof.

14. A pharmaceutical composition according to Claim 12, wherein the antimycotic drug comprises sodium pyrithione.

15. A method of treating conditions involving human nails, which comprises applying an effective amount of the composition claimed in Claim 9 to the affected nail or nails.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 86/02292

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (4): A61K 7/043, 31/78, 31/44
U.S. Cl. 424/61, 81; 514/345, 781

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	424/61, 514/345, 781

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

CASOnline Database

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	JP, A, 59-216822 (KOSHIZU et al), 6 December 1984, see translation (English) of Example 1.	1-3,9-11 & 15
X	US, A, 3,749,769, (SUGIYAMA et al), 31 July 1973, see the entire document.	1-3,5 & 6
X/Y	EP, A, 5857, (LEUNG et al), 14 July 1982, See Abstract, pages 1,6, 8-12 and 27.	1-3,5,6 & 9-11 / 12-15

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
20 January 1987	22 JAN 1987
International Searching Authority [1]	**Signature of Authorized Officer** [20]
ISA/US	Jackie Stone Jackie Stone

Form PCT/ISA/210 (second sheet) (May 1986)

III. DOCUMENTS CONSIDERED T BE RELEVANT (CONTINUED FROM THE SEC ND SHEET)

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No [18]
Y	JUE et al, "Ciclopirox Olamine 1% Cream, A Preliminary Review of its Antimicrobial Activity and Therapeutic Use" Drugs, Volume 29, issued 1985, see pages 334, 335 and 37.	15

FURTHER INFORMATION CONTINUED FROM THE SEC ND SHEET

Y	Chemical Abstracts, Volume 94, issued 1981 (Columbus, Ohio, USA), J.D. Nelson et al, "Sodium and Zinc Omadine Antimicrobials as Cosmetic Preservatives", see page 375, column 1, abstract No. 162626b, Cosmet. Toiletries, 1981, 96(3), 87-90 (Eng).	11-14
X Y	US, A, 2,972,545 (BRISKIN), 21 February 1961, See columns 1 and 3.	1-3,5,6 & 9-11 12-15

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers .... because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

Each of the resins recited in claims 2-8; namely cellulose resins, ethylene oxide resins, acrylic acid and acrylate resins, vinyl resins, and polyvinyl pyrrolidone resins, taken with each of the drugs or classes of drugs recited in claims 11-14 constitutes a different invention.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

1-3, 5, 6, and 9-15

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☒ No protest accompanied the payment of additional search fees.